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Original Article

# Combined Application of Tranexamic Acid and Thrombelastography in Pediatric Epilepsy Surgery

Qing-Fang Duan[1*], Wen-Ya Fu[3*], Wei Xiao[1*], Jia-Jian Qi[1], Guo-Guang Zhao[2], Yong-Zhi Shan[2], Xiao-Tong Fan[2], and Tian-Long Wang[1]

## ABSTRACT

**Background:** Pediatric patients undergoing epilepsy surgeries are under high risks of bleeding, hemodynamic instability and complications related to transfusions. This study aimed to investigate whether combined application of tranexamic acid (TXA) and thrombelastography (TEG) in pediatric epilepsy surgery can decrease blood loss, transfusion requirements and post-operation complications.

**Methods:** Thirty-two pediatric patients undergoing elective epilepsy surgery were randomized into two groups. Group T (Group T=Group Treatment, n=16) was given a loading dose of 10 mg/kg TXA in 15 minutes and then maintained at the speed of 5 mg/kg/h, while Group C (Group C=Group Control, n=16) was given the same dosage of normal saline. TEG tests were performed at the beginning of surgery (T1), opening the dura mater (T2), closing the dura mater (T3) and the end of surgery (T4) in both groups. In Group T, transfusion decision was made according to TEG results; while in Group C, it was made by anesthetist's experience without knowing the TEG results. The volume of blood loss, blood transfusion, post-operative drainage and complications were recorded.

**Results:** In Group T, intraoperative bleeding volume was significantly lower than Group C ([8.23 ± 4.10] ml/kg vs [12.86 ± 5.30] ml/kg, P=0.010]), and subsequently the ratio of transfusion of red blood cells (RBC) (18.75% vs 56.25%, P=0.026), fresh frozen plasma (FFP) (32.15% vs 43.75%, P=0.465) were significantly reduced. Maximal amplitude (MA) value of TEG at T3 (Group T=[61.11 ± 4.58] mm vs Group C=[56.09 ± 8.03] mm, P=0.038) and T4 (Group T=[60.31 ± 6.23] mm vs Group C=[54.08 ± 7.28] mm, P=0.014) in Group T were significantly higher than those in Group C. A significant difference existed between two groups in postoperative drainage volume in the first 24 hours (Group T=[4.19 ± 1.55] ml/kg vs Group C=[5.83 ± 2.07] ml/kg, P=0.017). Postoperative hospital stay was significantly shortened in Group T, compared to Group C ([7.9 ± 2.1] days vs [10.8 ± 3.8] days, P=0.014). No transfusion related complications occurred in both groups.

**Conclusions:** Combined application of TXA and TEG in pediatric epilepsy surgery may decrease blood loss, reduce transfusion requirements. The risk of thromboembolism may not be increased.

From [1]Department of Anesthesiology, [2]Department of Neurology, Xuanwu Hospital, Beijing, China; [3]Department of Anesthesiology, Beijing Children's Hospital, Capital Medical University, Beijing, China.

[*]Contributed to the work equally.

**Correspondence** to Dr. Tian-Long Wang at w_tl5595@hotmail.com.

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Epilepsy is a chronic neurological disorder (1). Surgery is the most effective way to control seizures in drug-resistant focal epilepsy, and surgery may results in improvements in cognition, behavior and quality of life, especially in children (2). Because the head of children accounts for 19% of the body, compared to 19% in the adults, a large percentage of cardiac output is directed to the brain and results in greater cerebral blood volume, compared to adults; meanwhile children have less autoregulatory reserves and less blood volume. These factors place the infants at risk for significant hemodynamic instability during neurosurgical procedures, as compared to adults (3). Besides, long term antiepileptic drugs (AEDs) taken often cause coagulopathies, such as hypofibrinogenemia (4). Therefore pediatric patients undergoing epilepsy surgery are under high risks of bleeding, hemodynamic instability and coagulopathies. Coagulation management is thus very essential in pediatric epilepsy surgery to maintain hemodynamic stability, reduce allogenetic transfusion and decrease corresponding complications.

Lacking of timely and accurate monitorings of coagulation status in this kind of surgery, component blood transfusion had to rely on anesthetists' experience. Relying on prothrombin time (PT) and active partial thromboplastin time (APTT) tested prior to operation may result in misunderstanding of coagulation status, because they could not reflect the whole coagulation process and timely coagulation status during operation.

Thrombelastography (TEG) plays an important role in perioperative transfusion guidelines, and has been proven useful for rapid assessment of homeostasis in patients with coagulopathy (5-8). TEG permits characterization of clotting process in whole blood by visualizing the viscoelastic changes that occur during coagulation in vitro, then provideing a graphical representation of the fibrin polymerization process.

Tranexamic acid (TXA) is a potent antifibrinolytic drug that prevents plasminogen activated by plasminogen activator (9). It is useful in the treatment of bleeding, without increasing the risk of thromboembolism in adult cardiac surgery, knee replacement surgery, and hip fracture surgery (10-12), as well as in pediatric cardiac surgery, spine surgery and craniosynostosis surgery (13-15).

The main goal of this study is to investigate whether combined application of TXA and TEG in pediatric epilepsy surgery can decrease blood loss, transfusion requirements and post-operation complications.

## MATERIALS AND METHODS

### Patients and Ethical Approval

The study was conducted at the Department of Anesthesiology, Xuanwu Hospital, Beijing, China, from 1 June 2014 to 31 March 2016, after obtaining approval from the Ethic Committee of Xuanwu Hospital and informed consents signed by patients' guardians.

Thirty-two pediatric patients aged 1-10 years, graded as American Society of Anesthesiologists physical status (ASA) I-II, scheduled for elective epilepsy surgery under general anesthesia were randomized by random number table to Group T (Group T=Group Treatment, n=16) and Group C (Group C=Group Control, n=16, Figure 1). Patients with hepatic dysfunction, renal dysfunction, blood disease, family history of hemorrhagic disease, allergies history of TXA or operation duration was less than 3 hours or over 8 hours were excluded. Cases undergoing a second surgery because of severe post-operative complications were removed from the study.

### Anesthesia Process

All patients received general anesthesia. Electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation ($SpO_2$), end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) and nasopharyngeal temperature (NT), invasive blood pressure (IBP) and pulse pressure variation (PPV), central venous pressure (CVP) were continuously monitored via a multifunctional monitor (AS/5, Datex-Ohmeda, Finland). Sedation depth was monitored by bispectral index (BIS, Covidien, MA, USA) and maintained between 40 and 60 during surgery. NT was controlled between 36℃ and 37℃ by an automatic heating blanket and heated air device. Ketamine of 5-7 mg/kg was injected intramuscularly prior to induction if patients can't cooperate with anesthetists. Otherwise, uncooperative patients were induced by inhalation of 8% sevoflurane in 8 l/min fresh gas for 5 minutes. After ve-

nous access in the upper limb was obtained, anesthesia induction was performed with propofol of 1-2 mg/kg, fentanil of 3 μg/kg, and rocuronium of 0.6 mg/kg, and then endotracheal intubation was performed. Patients were ventilated with 50% oxygen in air. Tidal volume was set as 8-10 ml/kg, and I:E ratio was 1:2. $P_{ET}CO_2$ was maintained between 30 mm Hg and 35 mm Hg. Anesthesia was maintained with a continuous infusion of propofol (6-8 mg/kg/h) and remifentanyl (0.2-0.4 μg/kg/min). Goal directed fluid therapy (GDFT) strategy was employed during operation to maintain the PPV value between 13%. Postoperative analgesia was carried out by intravenous parecoxib sodium (1 mg/kg) and 0.25% ropivacaine was used as local infiltration anesthesia at the incision site.

## Coagulation Management

TEG analyses (CFMS TM, Sinopharm Cmic, Beijing, China) was used to guide clotting factors supplement. TEG curve reflects different phases of the clotting process. The parameters used in this study are defined as follows: R (reaction/clotting) time is the period from the initiation of test till the beginning of the clot formation, reflecting coagulation factor activities. The α-angle is the angle between the baseline and the tangent to the TEG curve through the starting point of coagulation (the split after the end point of the R-time), indicating shortage of fibrinogen (Fib). Maximal amplitude (MA) is a direct measure of the highest point on the TEG curve and represents clot strength. Low MA means reduced platelet function. Ly30 is calculated on basis of the reduction in the area under the curve, which reflects fibrinolysis (6).

At the beginning of surgery, Group T was given TXA at a loading dose of 10 mg/kg in 15 minutes and then maintained at the speed of 5 mg/kg/h; while Group C was given the same dosage of normal saline. TEG and blood gas analysis were taken at the following time points: the beginning of surgery (T1), opening the dura mater (T2), closing the dura mater (T3) and the end of surgery (T4) in both groups. As T1-T4 were the key procedures of the surgery and between T1-T4 were the main procedures causing bleeding.

Transfusion strategy of fresh frozen plasma (FFP), platelet (PLT), and Fib was made by experience according to evaluated volume of blood loss and blood gas results, without knowing the TEG results in Group C. While in Group T, it was made according to TEG results : 1) if R>8 minutes, FFP of 8 ml/kg was transfused; 2) when α-angle<53°, Fib of 15 mg/kg was given; 3) if MA<50 mm, platelet concentrates of 1 unit was infused.

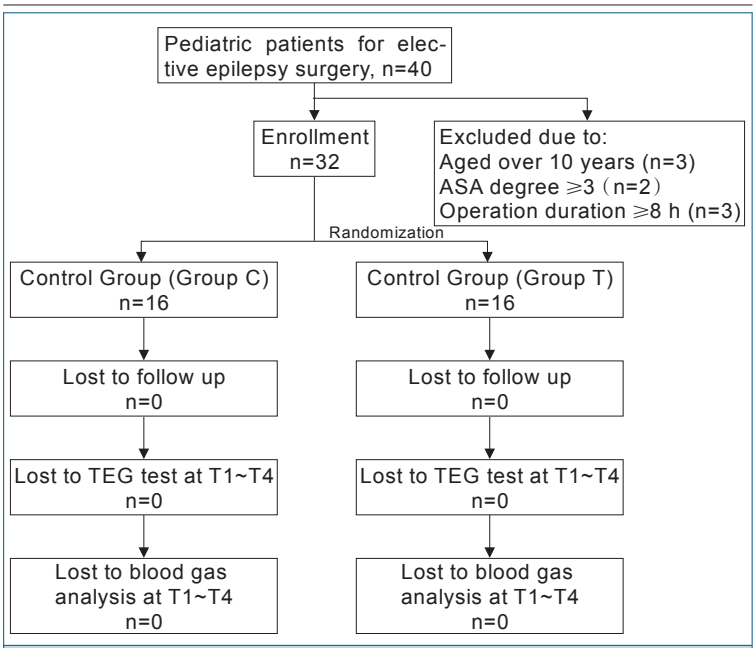


**Figure 1. Flowchart of This Study.**
ASA, America Society of Anesthesiologist; TEG, thrombelastography; T1, the beginning of surgery; T2, opening the dura mater; T3, closing the dura mater; T4, the end of surgery.

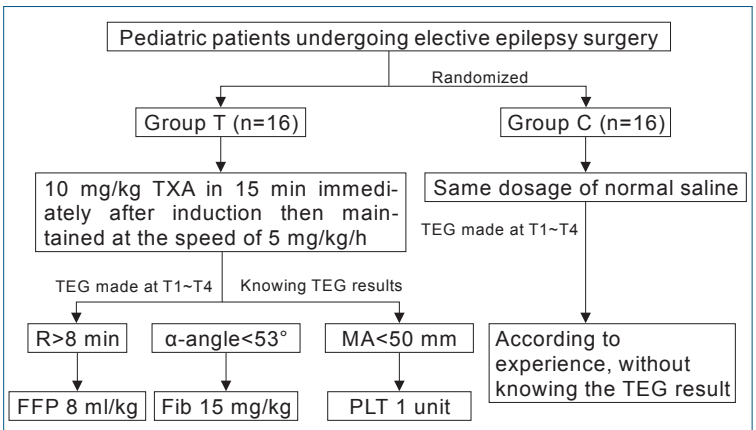


**Figure 2. Protocol for Coagulation Management in Pediatric Elective Epilepsy Surgery.**
TXA, tranexamic acid; TEG, thrombelastography; T1-T4 represent the beginning of surgery (T1), opening the dura mater (T2), closing the dura mater (T3) and the end of surgery (T4) respectively; R, reaction/clotting time; α-angle, the angle between the baseline and the tangent to the TEG curve; MA, maximal amplitude; FFP, fresh frozen plasma; Fib, fibrinogen; PLT, platelet.

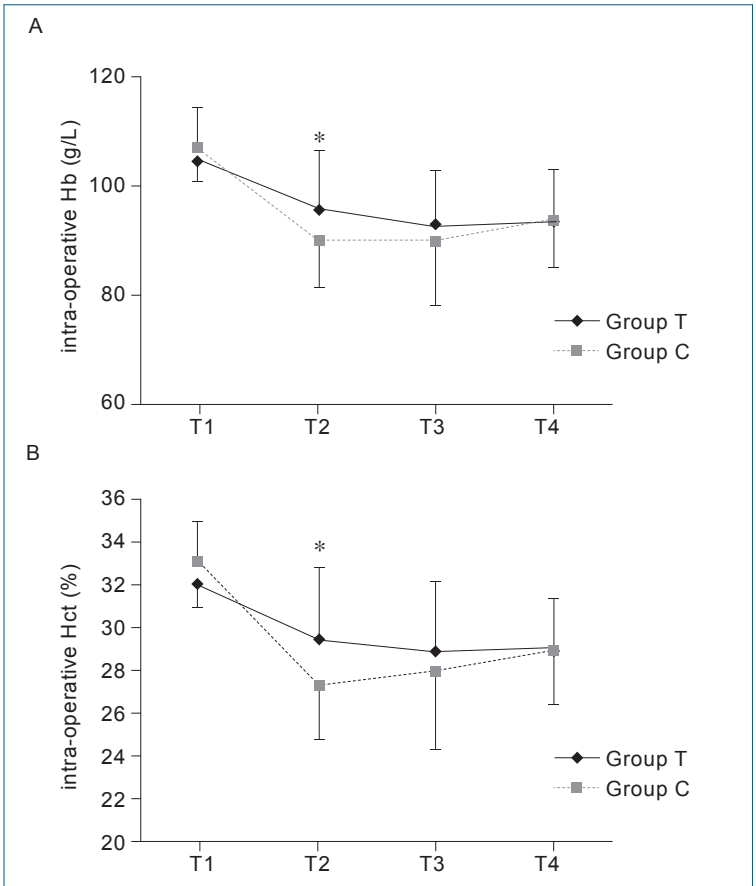


**Figure 3. Comparisions of Hemoglobin Level (A) and Hematocrit (B) between Groups during Operation.**
T1-T4 represent the beginning of surgery (T1), opening the dura mater (T2), closing the dura mater (T3) and the end of surgery (T4) respectively; Hb: hemoglobin level, Hct: hematocrit. Compare to Group C, *P<0.05.

**Table 1. Demographic Data and Anesthesia Characteristics.**

| | Group T | Group C | P value |
|---|---|---|---|
| Gender (Male/Female) | 8/8 | 10/6 | 0.476 |
| Age (yr) | 4.44±2.80 | 4.00±2.28 | 0.632 |
| BMI (kg/m$^2$) | 16.58±2.13 | 17.09±2.17 | 0.560 |
| ASA (Ⅰ/Ⅱ) | 10/6 | 12/4 | 0.446 |
| Surgery time (minutes) | 309.81±92.16 | 332.25±88.08 | 0.704 |
| Frontal lobo resection (%) | 37.5 | 43.8 | 0.719 |

Measurement data were expressed as means ± SD (n=32). $\chi^2$ test was used for analysis on gender ratio and frontal lobotomized.

Red blood cells (RBC) were transfused when hemoglobin (Hb) in blood gas analysis was less than 70 g/l or circulatory instability in both groups.

The primary endpoints of this study were blood loss and transfusion requirements. The secondary endpoints were postoperative hospital stay and relative complications. The volume of blood loss, blood transfusion, post-operative drainage and complications were recorded. The results of TEG test and blood gas analysis at T1-T4 were recorded, so were blood routine examinations and coagulation tests piror to and following operation.

## Statistical Analysis

*Sample Size Calculation*

According to the preliminary experiments in 2012-2014 in our Hospital, a sample size of 13 patients per group would give a power of 90% at a level of 0.05 to detect 30% or more reduction in allogenetic transfusion, which was 41% in pediatric elective epilepsy surgery. 32 patients were recruited to compensate any exclusion. Data are presented as means ± standard deviation or medians with ranges, 25% and 75% percentiles.

*Data Analysis*

Statistical analysis was performed with SPSS19.0. All quantitative data were evaluated for Gaussian distribution and homogeneity before statistical analysis. Mann-Whitney U-test was used intra and between groups with non-normally distributed quantitative data. Normally distributed quantitative data was analyzed by unpaired t-test with between groups, and One-way ANOVA intra-group. $X^2$ test was used for categorical data. P< 0.05 was considered as a statistical significance.

## RESULTS

32 pediatric patients undergoing elective epilepsy surgery (frontal lobe resection or temporal lobe resection) were recruited and randomized into two groups. There is no significant difference in general condition (Table 1), pre-operative Hb, pre-operative hematocrit (Hct) or baseline coagulation function (Table 2). The incidence of fibrinogen inefficiency was 31.25% and 37.50% in Group T and Group C individually (P=0.710).

Intra-operative blood gas analysis showed a significant difference in Hb ([95.56 ± 10.95] g/L vs [88.44 ± 8.25] g/L, P=0.046) and Hct ([29.55 ± 3.35]% vs [27.38 ± 2.53]%, P=0.047) tested when opening the dura mater (T2) (Figure 2, Figure 3). TEG showed similar results at the end of surgery (T4) compared to the beginning of surgery (T1) in both groups, except MA values at T4 were significantly decreased com-

pared to values at T1 in Group C (T4=[54.08±7.28] mm vs T1=[58.36±7.78] mm, P=0.039). Compared to Group C, MA values at closing the dura mater (T3) (Group T=[61.11±4.58] mm vs Group C=[56.09±8.03] mm, P=0.038) and T4 (Group T=[60.31±6.23] mm vs Group C=[54.08±7.28] mm, P=0.014) were significantly higher in Group T (Table 3). Intra-operative blood loss was significant less in Group T ([8.23±4.10] ml/kg vs [12.86±5.30] ml/kg, P=0.010). Therefore, the transfusion ratio and volume of RBC and FFP were subsequently lower in Group T (Table 4). There was no PLT transfused in both groups. No differences exist in fib transfusion between groups (Table 4).

Post- operative blood routine examinations showed similar results compared to pre-operative examinations except for lower PLT counts, especially in Group C ([244±69.31]×$10^9$/L vs [190±71.90]×$10^9$/L, P=0.041, Table 5). Postoperative values of PT, APTT and fibrinogen (Fib) were significantly increased when compared with pre-operative results (Table 6). A significant difference existed in Fib level between groups. 3 cases of hypofibrinogenemia happened in Group C, but no one in Group T (Table 6). Postoperative drainage volume was obviously different between the two groups in the first 24 hours following surgery (Group T=[4.19±1.55] ml/kg vs Group C=[5.83±2.07] ml/kg, P=0.017). Postoperative hospital stay was shortened significantly in Group T, when compared with Group C ([7.9±2.1] days vs [10.8±3.8] days, P=0.014). No complications occurred in both groups, such as thromboembolism, allergy or transfusion-related lung injury.

## DISCUSSION

Epilepsy is a chronic neurological disease and may impair cognition progressively. For refractory epilepsy, surgery is indicated (1). Patients undergoing epilepsy surgery suffering long period of operation and extensive insult, are under high risks of blood loss, coagulopathy and transfusion related complications, especially in children who have less blood volume and inadequate automatic circulatory regulation. AEDs taken before surgery also result in coagulation dysfunction, such as thrombocytopenia, abnormal platelet function and hypofibrinogenemia

**Table 2. Blood Routine Examination and Coagulation Function Test Pre-Operation.**

| | Group T | Group C | P value |
|---|---|---|---|
| Hb (g/L) | 120.63±14.33 | 124.69±10.64 | 0.370 |
| Hct (%) | 35.15±3.67 | 36.37±3.11 | 0.319 |
| PLT (*$10^9$/L) | 281.00±72.42 | 279.88±97.73 | 0.971 |
| PT (s) | 13.51±0.65 | 13.81±0.67 | 0.207 |
| APTT (s) | 39.46±2.03 | 38.61±1.76 | 0.215 |
| Fib (g/L) | 2.47±0.65 | 2.24±0.50 | 0.265 |

Measurement data were expressed as means±SD (n=32). Hb, hemoglobin; Hct, hematocrit; PLT, platelet; PT, prothrombin time; APTT, active partial thromboplastin time; Fib, fibrinogen.

**Table 3. Intra-Operative TEG Results.**

| | | R(min) | K(min) | Alpha(°) | MA(mm) |
|---|---|---|---|---|---|
| Group T | T1 | 7.15±2.10 | 2.33±0.71 | 65.80±5.82 | 59.30±8.71 |
| | T2 | 7.16±1.86 | 2.41±0.93 | 65.23±5.16 | 58.98±7.89 |
| | T3 | 6.33±1.59 | 2.01±0.31 | 68.03±3.84 | 61.11±4.58[b] |
| | T4 | 6.26±1.12 | 2.04±0.45 | 67.99±4.07 | 60.31±6.23[b] |
| Group C | T1 | 6.80±1.26 | 2.39±0.60 | 65.38±4.85 | 58.36±7.78 |
| | T2 | 7.19±2.72 | 2.33±0.64 | 65.62±5.10 | 57.48±6.52 |
| | T3 | 5.90±1.47 | 2.08±0.53 | 67.00±4.40 | 56.09±8.03 |
| | T4 | 6.06±1.64 | 2.27±1.19 | 64.63±9.06 | 54.08±7.28[a] |

The beginning of surgery (T1), opening the dura mater (T2), closing the dura mater (T3) ,the end of surgery (T4); [a]P<0.05 (compared to T1); [b]P<0.05 (compared to Group C).

**Table 4. Volume of Intra-Operative Blood Loss and Intra-Operative Transfusions.**

| | | Group T | Group C | P value |
|---|---|---|---|---|
| Blood loss (ml/kg) | | (8.23±4.10) | (12.86±5.30) | 0.010 |
| Suspension red blood cells | Ratio of patients transfused (%) | 18.75 | 56.25 | 0.026 |
| | Infusion quantity per person (ml/kg) | 2.80 | 6.89 | 0.054 |
| FFP | Ratio of patients transfused (%) | 31.25 | 43.75 | 0.465 |
| | Infusion quantity per person (ml/kg) | 3.07 | 3.38 | 0.573 |
| PLT | | 0(0) | 0(0) | 1.000 |
| Fib | Ratio of patients transfused (%) | 31.25 | 31.25 | 1.000 |

FFP, fresh frozen plasma; PLT, platelet; Fib, fibrinogen.

**Table 5. Blood Routine Examination following Operation.**

| | Group T | Group C | P value |
|---|---|---|---|
| Hb (g/L) | 93.69±11.14 | 98.00±17.78 | 0.418 |
| Hct (%) | 27.29±2.98 | 28.35±5.38 | 0.497 |
| PLT (*$10^9$/L) | 244.00±69.31 | 190.75±71.90 | 0.041[a] |

WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; PLT, platelet. [a]P<0.05 (compared to Group C).

**Table 6. Coagulation Function Test Comparison.**

| | Group T | | Group C | |
|---|---|---|---|---|
| | pre-operation | post-operation | pre-operation | post-operation |
| PT (s) | 13.51±0.65 | 14.25±0.86[a] | 13.81±0.67 | 14.78±1.39[a] |
| APTT (s) | 39.46±2.03 | 41.04±1.83[a] | 38.61±1.76 | 40.12±1.81[a] |
| Fib (g/L) | 2.47±0.65 | 3.39±1.06[ab] | 2.24±0.50 | 2.61±0.82 |

PT, prothrombin time; APTT, active partial thromboplastin time; Fib, fibrinogen. [a]P<0.05 (compared to pre-operation); [b]P<0.05 (compared to Group C).

(16- 19). Besides, extensive tissue injury of the surgery induced large amount of tissue activators of fibrinolytic system, which leads to hyperfibrinolysis. Thus, reducing transfusions and related complications by coagulation management is essential in pediatric epilepsy surgery.

Current strategy of transfusion is almost relying on anesthetists' experience and laboratory examination. RBC was transfused when Hb was less than 70 g/L, and FFP administered only when PT and APTT are >1.5 times the normal value. PLT transfusions may be indicated to maintain concentrations greater than $50 \times 10^9$/l (20). However, tests taken after massive bleeding, leading to delayed transfusion, and PT, APTT or PLT tested pre- operatively could not reflect whole procedure of coagulation. It's difficult to reduce transfusion and complications caused by massive blood loss, such as low body temperature, circulatory failure, coagulopathy, allergy, pyrexia, or infectious disease, etc (21).

TEG gives us a new choice in pediatric coagulation management. It could reflect whole procedure of coagulation and fibrinolysis, and thereby provides a global assessment of haemostatic function. The technology is based on measurements of the viscoelastic changes associated with fibrin polymerization that are happening during coagulation of a whole blood sample in vitro. The viscoelastic changes are recorded and finally converted to a curve. It may help doctors evaluate coagulation fuction to decrease the risk for bleeding and reduce the allogeneic blood transfusion in cardiac surgery with cardiopulmonary bypass and in liver surgery (6, 22- 24). TXA reversibly blocks the lysine binding sites of plasminogen, prevents activation of plasmin and stops lysis of polymerized fibrin. When massive blood loss is expected, prophylactic use of TXA can be a part of blood conservation strategy (9, 25). TXA prevents massive bleeding caused by AED related hypofibrinogenemia and surgery related hyperfibrinolysis, without increasing the risk of thromboembolism. However, few researches revealed pharmacokinetics and dosage regimen of TXA in pediatric patients. We used a TXA loading dose of 10 ml/kg and followed by continuous infusion of 5ml/kg/h, which was recommended by pharmacokinetic modeling (15, 26). Our results suggested combined application of TXA and TEG in pediatric epilepsy surgery may decrease perioperative hemorrhage and allogeneic blood transfusion ratio, which was consistent with the previous studies performed in other kinds of surgeries. In a case report with 3 pediatric patients undergoing elective hemispherectomy, using the same dosage of TXA together with hourly TEG results, observed a decrease in transfusions than reported (27). There was no significant difference in RBC and FFP transfusion volume per kilogram, and further study with enlarged sample size was indicated. Evenmore, in our study, as revealed by the TEG results, no hyper coagulative status was induced by this strategy. Post-operative seizures were less than pre-operation apparently.

No death occurred in 32 pediatric patients during hospital stay; postoperative hospital stay was shortened significantly in Group T. It suggested combined application of TXA and TEG may contribute to better postoperative recovery. Further studies were indicated.

Although our study suggested combined application of TXA and TEG in Group T may have many advantages over Group C, there are still some limitations. Firstly, this study was performed only in one center and the sample size was small. It may cover some side effects of our strategy. Secondly, this study recruited patients undergoing resection of frontal and temporal lobes. Although patients were randomized into two groups, the difference of excision location and size may still influence volume of blood loss. Thus, further study should enlarge the sample size to eliminate the difference and explore long-term effects.

## CONCLUSIONS

Infusion of TXA and TEG guided coagulation management in pediatric epilepsy surgery may decrease blood loss, reduce transfusion requirements and shorten postoperative hospitalization. This strategy may not increase the risks of thromboembolism.

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